

Amendments to the Specification:

Please replace the paragraph beginning at page 21, line 29 and extending to page 22, line 11, with the following amended paragraph:

FIG. 5 FIGS. 5A and 5B: ACE analysis of the interactions between peptides containing heparin-binding consensus sequences and HUVEC PGs. ACE gel images as obtained by a phosphorimager in which (A) (FIG 5A) EC PGs/GAGs or (B) (FIG 5B) heparin was fractionated through peptides. In (A) FIG 5A, at least two populations of high affinity PG/GAG, seen as two bands of radiolabeled material migrating with different mobilities, is visible at peptide concentrations of ≤ 50 nM. At a peptide concentration of 250 nM (near the $K_d \approx 300$ nM), a separation of the PG/GAG species is evident as a broad smear throughout the lane, and as a sharp band that migrates approximately half way down the lane, indicating heterogeneity in size, charge density and/or peptide binding interactions of the PG/GAG population. PG/GAG samples in which HSPGs have been chemically degraded by nitrous acid (EC PGs/NA), also displayed high binding affinity ($K_d \approx 300$ nM), implying that chondroitin/dermatan sulfates which remain in the sample bind the peptide strongly. In contrast to the heterogeneity seen in (A) FIG 5A, (B) FIG 5B shows that heparin migrates as a single broad band of radiolabeled material.

Please replace the paragraph beginning at page 22, line 21 and extending to page 23, line 11, with the following amended paragraph:

FIG. 7 FIGS. 7A-7J: Neutralization of Lovenox by Peptides in Vivo: Anti -Factor Xa Assay.
Neutralization of Lovenox by Peptides in Vivo: Anti -Factor Xa Assay

Absorbance @ 405 nm defines the heparin concentration in the plasma as a function of the amount of anti-Factor Xa activity. Heparin complexes with Antithrombin III and the complex inhibits Factor Xa. The amount of Factor Xa activity is determined by the change in A_{405} over 1 minute by chromogenic assay. The low point on each curve represents the highest amount of

anti-Factor Xa activity, a function of the highest concentration of heparin obtained in the particular animal. A₄₀₅ of 1.0 represents about 0.5U/ml of anti-Factor Xa activity, and A₄₀₅ of 0.5 represents about 1.0 U/ml anti-Factor Xa activity, based on standardization against Hepanorm low molecular weight heparin standards for the Stachrom Heparin kit. Administration of the peptide results in formation of a peptide/heparin complex, thus reducing the amount of ATIII-heparin complex and therefore reducing Factor Xa activity, resulting in reduced breakdown of the dye and return to baseline of the A₄₀₅. Rats were injected with Lovenox alone (Panel A) (FIG. 7A) or with Lovenox followed by peptide three minutes after injection of Lovenox (arrow) (Panels B-J) (FIGS. 7B-7J). Peptides were administered at 2 mg/300 gm animal except where noted otherwise. Blood samples (0.1 ml) were obtained for anti-Factor Xa analysis immediately before the injection of Lovenox, at 30-second intervals after the injection until 10 minutes, then at 1 minute intervals until 15 minutes, and at 5-minute intervals until 30 minutes.

Please replace the paragraph at page 41, lines 16-30, with the following amended paragraph:

Rats (300-400 gm) were anesthetized with ketamine/acepromazine and were cannulated in the left jugular vein and right femoral vein. Blood samples were all 0.1 ml. Blood was drawn immediately before injection of Lovenox to establish baseline Factor Xa activity. Lovenox (43 IU anti-FXa activity/kg in 0.1 ml saline, based on suggested dosage for humans) was injected through the jugular catheter, followed immediately by 0.2 ml of saline. Blood (0.1 ml) was collected into sodium citrate from the femoral vein every 30 seconds for 3 min. The peptide was injected at 3 min through the jugular catheter in 0.1 ml of phosphate-buffered saline, followed by a 0.2 ml saline flush. Peptides were administered at 2 mg except where noted otherwise. Blood collection was immediately resumed every 30 seconds until 10 minutes after the initial Lovenox injection, then at 15, 20, 25 and 30 min. The samples were centrifuged to obtain plasma and were assayed for residual Lovenox by assay of anti-FXa activity by the Stachrom

Heparin test kit. A405 was measured after a 1-minute incubation with the chromogenic Factor Xa substrate. The assay is described in further detail in the Figure Legend to Fig. 7 Figs. 7A-7J.

Please replace the paragraph at page 42, lines 2-5, with the following amended paragraph:

The animals appeared to tolerate the administration of the heparin and the peptide without obvious changes in heart rate and respiration. No animals died following administration of the peptides of interest in this application, although one animal died following administration of Protamine. The results are shown in Fig. 7 Figs. 7A-J.

Please replace the paragraph at page 42, lines 7-15, with the following amended paragraph:

The maximal concentration of Lovenox in the plasma was 0.1.0 U/ml anti-Factor Xa activity for all the animals tested. The maximal plasma heparin concentration was found by 2-2.5 minutes after injection. About half the Lovenox was cleared from the circulation by 25-30 minutes after injection, in an approximately linear fashion for 15 minutes and more slowly thereafter. Panel A Fig. 7A shows a representative clearance curve. The three peptides at dosages shown in panels B-D Figs. 7B-D caused no removal of Lovenox above that due to direct clearance from the circulation alone (Panel A) (Fig. 7A). The peptide (ARKKPAKA)₃ (Panel D) (Fig. 7D) appeared to delay clearance of the heparin from the circulation.

Please replace the paragraph at page 42, lines 16-21, with the following amended paragraph:

Protamine and three of our high affinity heparin-binding peptides [(AKKARA)₆, (ARKKAAKA)₅, and (ARKKAAKA)₄] neutralized the Lovenox concentration by at least 50%-80% within 2 minutes of injection of the peptide, the less tightly-binding mouse serglycin

Cardin-site peptide was somewhat less effective, and there was no further clearance of Lovenox in all cases for the remainder of the 30-minute experiment (Panels E-J) (Figs. 7E-J).